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Date: Thu, 21 May 1998 08:13:10 -0500
To: HV2B@nih.gov
From: "Collins, Francis (NHGRI)" <francisc@exchange.nih.gov> (by way of Richard Klausner)
Subject: FW:

Harold,
I am not sure that we will talk before the genome retreat and I won't be able to attend any of it. I am going to try to see if Harlow can attend for NCI.
I would like to be helpful and I think we need to be very careful here. If the motivation for NIH is competition, I think that we are on very thin ice and there will be very little buy in. Unfortunately, this is how it is sounding and it comes across in Phil's response to Francis' call for a science-based argument.
Changing the approach of the HGP is fine, but since it is reactive to Craig's announcement, the response has to be thoughtful, achieve broad consensus and not be rushed. I think the reasons for this are obvious but what happens when six months from now someone else announces a new venture (not unlikely) or what happens as Craig announces changes in his plans/approaches/business plans?
If the motivation is fear that Craig won't put things in the public sector, we have a paradox. If he does, great. If he doesn't, then,in some measure, it is as if his project doesn't exist and NIH proceeds.
All in all, there are real opportunities here. But, we must proceed cautiously and be sure what we want to do, recognizing that we can be profoundly reactive just so many times. My unsolicited advice to you is to seek quiet advice broadly .

Thanks for meeting with me on Monday, it was VERY helpful to get your reaction to possible plans. In follow up, I asked Phil Green to attempt some more sophisticated modelling efforts to predict the outcome of the Venter/Hunkapiller proposal. Here is his response. As you can see, he finds it extremely difficult to do this in a credible fashion. In fact, this is one of the major arguments against the whole genome shotgun strategy - until it's done (2 - 3 years from now) only God knows what the product will look like, and he ain't telling.
I thought you'd find Phil's perspective interesting.
Francis

-----Original Message-----
From: Phil Green [SMTP:phg@u.washington.edu]
<mailto:[SMTP:phg@u.washington.edu]>
Sent: Tuesday, May 19, 1998 11:52 AM
To: Collins, Francis (NHGRI)

Cc: bwaterst@watson.wustl.edu; <mailto:bwaterst@watson.wustl.edu;> agibbs@bcm.tmc.edu; <mailto:agibbs@bcm.tmc.edu;> elbert@alu.llnl.gov; <mailto:elbert@alu.llnl.gov;> jes@sanger.ac.uk; <mailto:jes@sanger.ac.uk;> lander@wi.mit.edu <mailto:lander@wi.mit.edu>

Subject: RE:

Francis,
Re your suggestion to do some modelling to bolster our case-
Unfortunately it really is impossible to do anything persuasive, both because we just do not know enough about distribution of repeats in the genome as a whole to make a believable model, and because as John points out their strategy is a moving target. Venter's strategy has been modified over the past week. The introduction of the 10 kb plasmids is already a major change, apparently to respond to the point about L1 elements. It brings their approach more in line with the original Weber-Myers proposal (which also used two size-classes of subclones), and incidentally makes it pretty clear to me at least that they had not read either the Weber-Myers paper or my rebuttal prior to it last week.
The strongest argument we have regarding feasibility, in lieu of a theoretical analysis, is simply the fact that there are individual BACs that are very difficult to finish, and when you go to a larger scale the problem obviously gets (much) worse, not easier. Many of these finishing problems still require a lot of human attention-there is no single panacea (such as forward-reverse reads, which have been in use for a long time) which makes the process algorithmic. Their budget does not include money to cover finishing on the scale required.
While we should avoid being unnecessarily confrontational, I do feel we have a responsibility as scientists to forcefully reject the fundamentally anti-scientific way in which Venter/Hunkapiller are going about things. Here they are proposing in the NY Times to drop the publicly funded project without even having thought about, or devised a plan to address, obvious technical difficulties that were pointed out in the scientific literature a long time ago. The major uncertainties in all this is one of the main things we should stress, and it wouldn't hurt to emphasize how much their strategy has changed (in major respects!) in the last week alone. Furthermore if their scientific plan can change that much in a short time, so can their business plan-and public release of the data has got to be viewed as by far the weakest aspect of their business plan. We might emphasize that their only real obligation regarding what they do is to the shareholders of P.E. and other investing companies, who might well object to giving away the data. We might also make the point that the issues here are broader than sequencing. Who is to say some company won't come along next week and say that they because they are thinking about starting a major functional genomics effort in (say) the mouse, the government should stop funding all research in this area? It could happen!
Phil